Electrophysiology and Density of Retinal Neurons in Mice With a Mutation That Includes the Pax2 Locus

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Purpose. The Krd mouse has a deletion in chromosome 19 that includes the Pax2 gene locus. The aim of this study was to characterize in detail how these retinas differ from normal.

Methods. Both electroretinographic and anatomic methods were used to assess visual function. Full-field flash electroretinograms (ERGs) and planimetric densities were obtained from Krd and control animals.

Results. Measurements of the ERG show that in the Krd mice, both a- and b-wave amplitudes are attenuated relative to control by amounts that vary from animal to animal. The b-wave of the ERG generally is affected more severely than the a-wave. However, there is little or no shift of the curves relating the b-wave and a-wave amplitude to the intensity of the stimulus. Also, no change in the response kinetics seems to be associated with the attenuated responses. Estimates of planimetric cell density in the outer nuclear, inner nuclear, and ganglion cell layers show significant cell losses in affected animals that are more pronounced proportionally in the inner layers. Comparisons between electrophysiological and histologic measurements made on each eye show good correlation between the reduction in the ERG components and the magnitude of cell losses.

Conclusions. These experiments show that the eyes of Krd mice have reduced ERGs and reduced cellular density. There is a loss of cells in all layers of the retina, but the inner layers are affected more severely. Consistent with this, the b-wave is reduced more than the a-wave. The normal functional dependency of the ERG on stimulus intensity and the normal response kinetics suggest the cellular losses are not associated with changes in cellular function. Invest Ophthalmol Vis Sci. 1997;38:919-929.

Murine models for human eye disease include mutants that have occurred spontaneously,1-4 those in which a specific gene has been targeted for mutation,5-11 and transgenic mouse lines expressing mutant proteins.12-17 Although descriptions of the molecular lesions define the ultimate causes of these developmental defects, elucidation of the functional significance of these lesions requires the application of techniques from cell biology. More specifically, electrophysiological and morphologic examination of such animals' retinas may provide the means to establish the functional consequences of particular mutations, the extent to which an animal model mimics human disease, and the underlying mechanisms that cause these diseases.

This article provides an example of such a study. We have characterized physiological and anatomic abnormalities in the retina of the Krd mouse, which are hemizygous for the developmental regulatory gene Pax2.18 These animals have kidney and retinal abnormalities and are of particular interest because Sanyanusin et al19,20 have described a human family with a mutation in PAX2 that has kidney abnormalities, low visual acuity, and optic disc abnormalities and thus phenotypically resembles the Krd mouse.21

In an earlier publication describing the genetic abnormality,18 we described briefly the alterations in the electroretinogram (ERG) and retinal anatomy in this strain of mutant mice. In this report, we use quantitative methods to describe in detail changes in the waveform of the ERGs from the Krd mouse and com-
A total of 18 mice, 8 Krd mice and 10 control animals, were used. The Krd mutation is a deletion in chromosome 19 (Del(19)TgN8052Mn) identified at the site of a transgene insertion.19 All Krd mice are heterozygous for the deficiency (hemizygous for Pax2). The transgene in this mouse line expresses the bacterial enzyme chloramphenicol acetyltransferase under the control of a pancreas-specific enhancer element.22 Chloramphenicol acetyltransferase has been used as a reporter in a variety of tissues, including the retina,23 without apparent phenotypic consequences. The Krd mutation was discovered in a large-scale screen of many transgenic lines carrying similar or identical transgene constructs.24 The abnormalities associated with the Krd mouse are therefore most likely caused by the associated but unintended multicentimorgan deletion, which removes the Pax2 locus as well as other genes.18 The transgenic founder was generated by injection of fertilized eggs obtained from the cross of two (C57BL/6J × C3H/HeJ)F1 hybrids. First-generation offspring of the transgenic founder were produced by crosses to strain YBR/Ki. Subsequent generations were produced by crossing transgenic offspring to strain. C57BL/6J (obtained from the Jackson Laboratory, Bar Harbor, ME). The Krd animals used were third to fifth generation. Control mice were nontransgenic siblings. The animals were housed in well-lit animal rooms on a 12-hour light–12-hour dark cycle. At the time of the experiments, the animals ranged between 4 and 12 months of age. Experiments were carried out in accordance with the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research.

Stimulus

Light flashes (40-msec duration) were derived from 150-W xenon arc lamp. The white stimulus illuminated a ping-pong ball covering the eye. The duration of the stimulus was controlled by an electronic shutter (UniBlitz, Model VS25; Vincent Associates, Rochester, NY) under computer control. The intensity of the light could be changed in steps of 0.5 log unit by placing neutral-density filters in the beam. The unattenuated stimulus produced an intensity of 3.1 log cd/m² on the inside of the ping-pong ball. The maximum energy in the 40-msec shuttered flash was 1.7 log cd/s per m². The maximum energy that could be delivered during the first 10 msec was only approximately 0.7 log cd/sec per m², because the shutter has a 6-second opening time.

Recordings

Before each experimental session, the animal was dark-adapted for at least 12 hours and then anesthetized with injections intraperitoneally (0.1 ml/5 g) of Avertin (a 1.2% solution of tribromoethanol [Aldrich Chemical, Milwaukee, WI]). Supplementary doses of anesthetic were given as needed, usually every 30 minutes. The surgery and setup were done under dim red light. The eyelid of the experimental mouse was drawn back with silk sutures. The cornea was anesthetized with tetracaine (0.5%) and the pupil dilated with 1% atropine sulfate. The mouse was laid on its side with its head fixed in place with surgical tape and dark-adapted for an additional 10 minutes. ERGs were recorded between a small silver–silver chloride cotton-wick electrode that was placed near the vertex of the cornea and a stainless steel needle electrode (Grass, type E2) placed in skin over the nose. The wick was white and approximately 0.8 mm wide. Most of the light that struck it was scattered rather than absorbed. If a small portion of the incident light was blocked, this occurred in all the experiments.

To produce uniform stimulation of the whole retina, a half ping-pong ball was placed over the eye. Electrical potentials were recorded with an alternating current–coupled amplifier (bandwidth of 0.2 to 250 Hz). Single responses were digitized and stored using a computer-based data acquisition system (Labview; National Instruments; Austin, TX). Data were collected using a fixed stimulus set in which the intensity increased progressively in 0.5 log step. Low-intensity flashes were interposed between brighter flashes to ensure there was sufficient time between flashes for the prior sensitivity to be restored. After single flashes of less than 0.5 log cd/m², recovery was rapid. Sixty seconds was sufficient time for the measured response
amplitudes to be unaffected by earlier flashes. Recordings from normal and Krd animals were made in successive sessions. The peak amplitudes of the recorded ERGs were measured by fitting second-order polynomials to segments of the record containing each of the peaks, as discussed further by Green et al. The amplitudes of the first negative peak defined the a-wave amplitude. The voltage measured from the negative peak (a-wave) to the first positive peak defined the b-wave amplitude.

**Histologic Analysis**

Nine mice (eight Krd and one control) received a lethal dose of sodium pentobarbital and were perfused through the heart with a solution of 2.5% glutaraldehyde-2.0% paraformaldehyde in 100 mM phosphate buffer, pH 7.4. Eyes were enucleated, punctured through the cornea, and fixed overnight at 4°C. Each eye then was bisected through the dorsoventral axis, and half was dehydrated in alcohol, infiltrated, and cast in glycomethacrylate (Polysciences, Warrington, PA). Cross-sections through the eye were cut at 5 μm, mounted on poly-L-lysine-coated glass slides, stained with 2.5% toluidine blue, and coverslipped.

**Cell Counts**

We have used nonstereologic methods for estimating the planimetric density of neurons in normal and Krd animals and have made the following assumptions. First, the nuclei of retinal cells generally are spherical in shape. Second, nuclear shape does not vary systematically with density. Third, the errors in our estimations are smaller than the variations in cell density among the animals studied. Cell counts were made using methods described previously. Sections as close as possible to the dorsoventral axis of the eye were selected for cell counts. This helped ensure that sections oriented perpendicular to the retinal layers were sampled, thereby avoiding sampling sections passing obliquely through the retinal layers. Cell counts were taken from one section per eye. In each eye, two retinal sites, judged to be spaced equally on either side of the geometric center of the retina, were sampled. The center of the retina was not sampled because of the laminar malformations present commonly in the retinas of the Krd mice.

An image of each site sampled for cell counts was digitized at 900× magnification using a video camera interfaced with a Macintosh computer (Apple, Cupertino, CA). Each image represented a 220-μm length of retina, resulting in a total of 0.0022 mm² of the retinal surface being sampled for each retina (0.005-mm retinal thickness × 0.22-mm retinal length × two retinal sites). Cells in each image were visualized and counted using a Power Macintosh 8100/100 (Apple) and the public-domain National Institutes of Health (NIH) Image software (available from Internet by anonymous FTP from zippy.nimh.nih.gov or as part number PB95-500195GEI; Technical Information Service, Springfield, VA). Only cells that had a distinct cellular profile and, for the ganglion cell and inner nuclear layers (INLs), contained an obvious nucleolus were counted. For purposes of correcting the cell counts, nuclei were traced from the sites selected for the cell counts and nuclear diameters were measured using a digitizing tablet and NIH Image. Planimetric densities were computed by dividing the corrected number of neurons by the product of retinal length sampled and the section thickness (see above). No corrections were made for tissue shrinkage.

**RESULTS**

**Electroretinograms**

In the initial experiments, ERGs were measured on the right eyes of five control and eight Krd mice. The responses from the Krd animals varied from being nearly normal to being highly abnormal. Figure 1 summarizes this finding by showing ERGs recorded at various intensities from one control mouse (Fig. 1A) and from representative Krd animals (Figs. 1B, 1C, and 1D). The intensity of the stimulus ranged from quite
dim to quite bright (−1.9 log cd/m$^2$ to 3.1 log cd/m$^2$). Two Krd mice had nearly normal ERGs over the whole range of intensities. The response of one of these animals is shown in Figure 1B. The ERGs from the other six animals ranged from mildly abnormal to grossly abnormal. The responses in Figures 1C and 1D are examples of the varying severity in the affected animals. The b-waves in Figure 1C are approximately one-third normal size and in Figure 1D, they are nearly absent. Also clear from these records is the reduction in a-wave amplitude.

**Intensity–Response Functions**

Figure 2A shows the variation in the amplitude of b-wave response as a function of the flash intensity for all eight right eyes of the Krd mice. For comparison, the averages from the control mice (with standard errors) also are plotted. The amplitudes were extracted from responses such as those in Figure 1. It is clear that the amplitudes are attenuated in Krd mice by an amount that varied from animal to animal. However, there appeared to be little or no shift of the curves along the intensity axis. To confirm this, each of the data sets in Figure 2A were fitted with a rectangular hyperbola of the form $I/(I + \sigma)$, where $I$ is stimulus intensity. The fits were reasonably good as long as only the data at intensities below 1.5 log cd/m$^2$ were used. All the $\sigma$ values from the least-squares fitted curves were close to each other ($\log \sigma = −1.49 ± 0.20$ standard deviation (range, −1.04 to −1.65) log cd/m$^2$) with no obvious correlation between the degree of severity and $\log \sigma$.

Normalized response-intensity functions were plotted and are shown in Figure 2B. Each response was normalized by the amplitude of the response obtained at the highest intensity. When normalized, there is little or no difference in the shape of the normalized response-intensity functions, with the one most affected mouse being the possible exception. There is doubt about this animal because its responses were small and were dominated by the a-waves at higher intensities. Because we measured b-wave amplitudes from the peak of the negative potential, there is strong a-wave–b-wave interaction, so accurate measurements of b-wave amplitude may not have been obtained on this animal. As might be expected for such interactions, a dip in the curve occurs between 0 and 1 log cd/m$^2$, just where the growing a-wave would cause the amplitude of the b-wave to be underestimated. The log $\sigma$ value from the best-fitting rectangular hyperbola, fitted to the lower intensity portion of this curve, was −1.62 log cd/m$^2$.

Figure 3 shows the amplitudes of a-wave response as a function of flash intensity for control and Krd
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FIGURE 3. Amplitude of a-wave responses as a function of the flash intensity. (A) The amplitudes of the a-waves in each of the Krd mice (symbols as in Fig. 2). (B) Normalized a-wave responses. The a-waves from each of the mutant mice, normalized by the response at the highest intensity. (C) A-wave amplitudes at a fixed time of 16 msec after the start of the flash. The responses have been normalized by the response at the highest intensity. (D) The responses to the maximum flash intensity from A and D of Figure 1. The response to the Krd animal has been scaled in amplitude by a factor of 3.

In Figure 3A, the actual a-wave response amplitudes are plotted. As with the b-wave, the a-wave amplitudes are attenuated in Krd mice. When the responses are normalized by the response at the highest intensity, there is little or no difference in the shapes of the response-intensity functions (Fig. 3B). The amplitude of the a-wave might not be a good measure of receptor activity, because it is determined by interactions between underlying PII and PHI components. Consequently, we also measured a-wave amplitudes at a fixed time.

The results of this analysis (Fig. 3C) indicate that in all the animals, the a-waves grew in a similar manner with increasing stimulus intensity. In Figure 3D, this finding is illustrated in another way. On an expanded time scale, the responses to the maximum flash intensity of Figures 1A and 1D are shown, with the response from the Krd animal scaled by the amount necessary to get the results in Figures 3B and 3C. Note that the leading edges of the a-waves agree quite well after scaling. Figure 3D illustrates another aspect of our responses, which is that b-wave amplitudes were reduced more than were a-wave amplitudes. The ERG in Figure 3D from the Krd animal is a predominately negative response, with the b-wave suppressed greatly relative to the a-wave. To illustrate the generality of this finding, in Figure 4, we have plotted the a-wave/b-wave ratio, defined by dividing the maximum a-wave amplitude by the maximum b-wave amplitude, against the b-wave amplitude. In normal animals at high-flash intensities, the b-wave is twice as large as the a-wave (a/b = 0.5). In the severely affected animals, the a-wave and b-wave are approximately equal in size (a/b ≈ 1), showing clearly that the retinal defects affect the a-wave less than they do the b-wave.

Kinetics and Implicit Time Relations

The agreement of the normalized b-wave response amplitudes, shown in Figure 2, suggests that the b-waves in the Krd animals simply are smaller than normal at all stimulus intensities. If this is true, then after normalization, the time course of the responses in the Krd animals should be the same as that in the normal animals. Therefore, we compared the implicit times, the time from the start of the flash to the peak of the b-wave in normal and Krd animals. Figure 5 shows the time to peak of the b-wave response as a function of the flash intensity.
FIGURE 4. Ratio of the a-wave amplitude to the b-wave amplitude as a function of b-wave amplitude. The open circles are from electroretinograms obtained on the left eye and the closed circles from right eye measurements. A smooth curve has been drawn through the points. Ratios from control animals are indicated with filled triangles.

for normal (solid line with standard deviation bars) and mutant mice. Consistent with there being a simple attenuation of responses, the b-wave implicit times of all of mice decreased similarly with increasing light intensity. Next, we attempted to compare the actual shapes of the responses to determine if they were the same. Making this comparison directly is complicated by the change in a-wave/b-wave ratio in the affected mice (Fig. 4). We have tried to circumvent this in two ways. First, we compared low-level responses, where there are no a-waves. Figure 6A shows the same sample low-level ERGs as in Figure 1 but with the b-waves normalized to the same peak (I = −0.9 log cd/m²). The solid curve is the normal animal. The responses are reasonably similar to each other. The possible exception is the animal affected most severely. Given the small size of the responses and the underlying noise of the recordings, we cannot say, with confidence, that kinetics of responses in the severely affected mouse are different from those of the normal mouse. Second, we attempted to remove the a-wave component of the responses from high-level responses. To do this, we used a computational model, similar to that used by Hood and Birch,30,32 to calculate the time course of PIII from the leading edge of the a-wave for the high-intensity responses in Figure 1. The receptor response was modeled by a linear filter with a flash response having a fixed shape, \[ g(t) = a_1(t^2e^{-11.8t}). \] This was followed by a hyperbolic saturation of the form \[ a_2 = \frac{g}{g + 1}. \] A least-squares search procedure was used to find the values of \( (a_1, a_2) \) that gave the best fit to the leading edge of the a-wave. The parameters for the receptor responses fitted to the records in parts A to D of Figure 1 were (49.5, 0.717), (22.7, 1.02), (32.2, 0.463), and (20.1, 0.287), respectively. These calculated PIII then were subtracted from each of the responses,30 and the resulting responses were normalized to the same peak. As Figure 6B shows, the b-waves derived in this manner have similar time courses. Thus, we conclude that at all intensities, b-wave kinetics in the control and Krd animals were in reasonable agreement.

Histologic Analysis and Neuronal Planimetric Density

As reported previously,18 we observed a panretinal hypocellularity in the retinas of the Krd mice that varied markedly in degree between mice. Figure 7 illustrates photomicrographs taken from the eyes whose ERGs are illustrated in Figure 1. Panels A to D are representative of the range in retinal morphology and the relatively greater variation in the density of neurons in the ganglion cell and INLs. Figure 8 shows
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Quantitative data on the planimetric densities of the Krd mice for neurons in the outer nuclear layer (ONL), INL, and ganglion cell layer (GCL). For ease of comparison, the respective densities have been normalized by 260,000 (ONL), 58,410 (INL), and 6955 (GCL), respectively, the average planimetric densities of the control animals. The normalized values are plotted against the total thickness of the retina, a reasonable measure of the degree of severity. The lines show the best least-squares fits to the three

Figure 6. Comparison response kinetics. (A) Comparison of the sample responses from normal (solid line) and Krd (dashed and dotted lines) mice at low (–0.9 log cd/m²) intensity. Each response is normalized by its peak. (B) Comparison of the b-waves from normal (solid line) and Krd (dashed and dotted lines) mice at high (3.2 log cd/m²) intensity. All the tracings are derived from the response sets shown in Figure 1.

Figure 7. Photomicrographs (A to D) taken from the eyes whose electroretinograms are shown in Figure 1. The scale bar is 50 μm.
sets of data. In general, in the most severely affected animals, the density of ONL cells was reduced to approximately half of normal density, the INL to a third of normal density, and the GCL to a fifth of normal density. Consistent with a greater effect on the b-wave than the a-wave, there is a much greater loss in the inner than in the outer retina.

Comparison of Electrophysiology and Histology

How well does the histology and electrophysiology agree? In Figure 9A, outer segment length is plotted against a-wave amplitude. If there was any change in outer segment length in affected animals, it was quite small. The correlation between outer segment length and a-wave amplitude is weak (R = 0.486). Planimetric densities of ONL cells are plotted against the amplitudes of the a-wave of the ERG in Figure 9B. In Figure 9C, the densities of INL cells are plotted against the amplitudes of the b-wave of the ERG. In the parts B and C plots, there is a clear relation between cell density and ERG amplitude. The plot of density of photoreceptors versus the a-wave amplitude had an R value of 0.724. Similarly, the plot of INL cells versus b-wave amplitude had an R value of 0.878.

FIGURE 8. Planimetric densities of the Krd mice for neurons in the outer nuclear layer (ONL-○), inner nuclear layer (INL-□), and ganglion cell layer (GCL-△) versus retinal thickness, measured from outer- to inner-limiting membranes. The densities have been normalized by the average planimetric densities of 260,000 (ONL), 58,410 (INL), and 6955 (GCL) from the 2 normal retinas. The measurements come from the left and right eyes of eight Krd mice and a control mouse. Normal retinas are shown with solid symbols. The lines were least-squares fitted to each of the three sets of data.

FIGURE 9. Comparison of histology and electrophysiology. (A) Outer segment length and a-wave amplitude. The best fitting line is shown (R = 0.486). (B) The planimetric densities of the outer nuclear layer cells are plotted against the amplitudes of the a-wave of the electroretinogram (ERG). The average amplitude of the a-wave in the control animals was 0.688 mV. The line was fitted by least squares (R = 0.724). (C) The densities of inner nuclear layer cells are plotted against the amplitudes of the b-wave of the ERG. The best-fitting line is shown (R = 0.878). The average control b-wave amplitude was 1.45 mV. The averages for normal retinas are shown with solid symbols.

Age

The question of whether the defects in Krd mice are progressive is of some interest. To address this issue, we have plotted both the density of INL cells and the amplitude of the b-wave response to the highest intensity flash as a function of the age of the animals (Fig. 10). In the Krd animals, there appears to be a systematic fall in INL density and b-wave amplitude with age. These plots provide evidence that the Krd defects seem to progress with increasing age. Compared with the data in Figure 10A, the plots of ONL density versus age showed a much weaker dependency and GCL density versus age showed a slightly stronger dependency on age (results not shown). We found no systematic age dependence in the amplitude of the ERGs from the control animals.
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![Graph showing progression with age. Density of inner nuclear layer cells (A) and b-wave amplitudes (B) are plotted as a function of the age of the animal. Krd animals are indicated with open symbols and control animals with solid symbols. Data from left and right eyes of Krd animals are plotted where available.]

DISCUSSION

We have described the retinal electrophysiology and morphology of a mouse with a deletion of chromosome 19 that includes the Pax2 locus. The homozygotes are not viable, so the data we present are from heterozygous animals. Pax2 is a homeobox gene that is expressed during fetal development in the kidney and optic cup. The known eye and kidney abnormalities in these animals are consistent with these features of Krd that are caused by the deletion of Pax2. The functional deficits associated with mutant eyes presumably are caused by reduced levels of Pax2 protein, and the subsequent failure to regulate transcription of downstream genes properly. Such haploinsufficiency, although relatively uncommon when all mouse mutations are considered, has been noted for all three of the other identified Pax mutations. Like the retinal defects, kidney structural abnormalities also were quite variable in extent, with only 25% of mutant animals showing gross kidney malformations.

Pax2 is a member of the Pax family of genes, which encode DNA-binding proteins and act as transcriptional regulators. The importance of Pax genes in development is inferred by their primary expression during embryonic development and their extremely high-sequence conservation between distantly related species. Each member of the Pax family is expressed in a spatially and temporally restricted pattern, suggesting these genes are involved in the control of tissue morphogenesis and pattern formation. Significantly, mutations of Pax genes in mice and humans result in similar phenotypes, which suggests that knowledge of mouse developmental biology can be used as a basis for understanding the action of Pax genes and their mutations in humans. The embryonic expression pattern of Pax2 in the mouse eye has been described, and the pattern of expression suggests this gene could play a role in ocular morphogenesis. Consistent with this, mutation or deletion of Pax2 results in autosomal-dominant malformations of the retina, optic disc, and optic nerve. Recently, a family with a point mutation of one allele of PAX2 was identified and described with autosomal-dominant optic disc colobomas. The visual acuity of the affected family members ranged from 20/100 to light and color perception only, suggesting they may have retinal abnormalities as well. These observations suggest that the Krd mouse may recapitulate the phenotype of humans with PAX2 mutations and reinforce the use of the Krd mouse as a model to investigate the functional deficits associated with human PAX2 mutations. Whereas the defects we see in the Krd mice may, in part, be caused by the deletion of genes other than Pax2, haploinsufficiency caused by loss of a single allele is characteristic of members of the Pax gene family, but rarely has been observed for other genes.

In the rod-dominated mouse retina, there are approximately 40X as many photoreceptors as there are ganglion cells. In achieving the exquisite photon sensitivity that these animals possess, it seems obvious that
convergence of photoreceptors onto second-order cells is important. However, it seems likely that the retina also requires a normal quorum of cells and associated functional architecture. Analysis of these animals allows us to assess retinas that have systematic alterations in the proportion of neurons present in the retina. It provides an opportunity experimentally to ask to what extent sensitivity and processing depend on the normal numbers of cells and their numerous parallel and feedback interactions. In this regard, the cause of the neuronal depletion is of secondary importance.

The full-field, flash ERG is the complex, summed response of the whole eye whose components arise from different cellular elements in the retina. The initial negative component, the a-wave, generally is agreed to originate from the mass response of photoreceptors, whereas the b-wave is related to the activity of the depolarizing bipolar cells of the INL of the retina. In the majority of Krd mice, there was a reduction in both a- and b-waves of the ERG. The extent of reduction in amplitude varied between eyes. Decreases in either of these waves could be a result of functional abnormality in these cells or a reduction in the number of cells. The similarities in the change of the response amplitude and response kinetics with stimulus intensity are consistent with those of simple transgenic animal Pax2, rhodopsin gene. In: Hollyfield JG, Anderson RE, LaVail MM, eds. Retinal Degeneration: Clinical and Laboratory Applications. New York: Plenum; 1993:211–217.

Key Words

cellular density, electroretinogram, Pax2, transgenic animal

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